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Systematic Review

Long-term indwelling urinary catheterization and bladder cancer

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ABSTRACT

Bladder cancer is cancer that originates from the bladder mucosa. The causes of bladder cancer are multifactorial. Long-term use of urinary catheters will increase the risk of bladder cancer. There has been no systematic review that discusses the association between indwelling catheters and bladder cancer. We aim to assess the association between long-term indwelling catheters and bladder cancer. We performed a literature search from PubMed/MEDLINE, Cochrane Library, and Scopus. The data included in the study were only observational studies that were relevant to the study objective. The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). The data was then synthesized using the Review Manager 5.4 application to determine heterogeneity and cumulative hazard ratio values. There were 640 studies obtained from the PubMed/MEDLINE, Cochrane Library, and Scopus databases. After removing 16 duplicated studies, there were 624 results left. Out of these studies, 6 qualified for systematic review. Data on indwelling catheters for bladder cancer are highly heterogeneous. The incidence of individuals with indwelling catheters with probable bladder cancer was 4.87% (95% confidence interval (CI), 1.7–13.96%, I2 = 84%). The use of indwelling catheters significantly increases the risk of bladder cancer (p=0.003). The bias assessed using the Newcastle Ottawa scale (NOS) showed a poor-quality result (4.83 final score). Long-term indwelling catheter are associated significantly with an increased risk of bladder cancer.

Keywords: Long-term indwelling catheter, Bladder cancer, Systematic review

INTRODUCTION

Bladder cancer is cancer that originates from the bladder mucosa (urothelium). Bladder cancer is the fifth most common neoplasm and the leading cause of cancer death in the United States. The annual incidence rate of bladder cancer based on age is 17 per 100,000 people.[1] In contrast, Chung et al. found that bladder cancer is the seventh malignancy that causes mortality in men worldwide. Worldwide data from GLOBOCAN revealed there are about 430,000 incident cases per year with 165,000 deaths. Several risk factors for bladder cancer include geriatrics, gender (male), smoking, exposure to aromatic amines in industrial settings, cyclophosphamide therapy, and schistosomiasis infection in endemic areas. Main risk factor for bladder cancer is tobacco smoking, associated with about 50% of all bladder cancer cases in men. Occupations at greatest risk of BC include those in paint, dye, rubber, metal, and petroleum industries.[2-5]

The mean age at initial diagnosis of bladder cancer was 53.3±14.7 years.[6] The most common histological type of bladder cancer is transitional cell carcinoma in approximately 90% of all cases, while squamous cell carcinoma (SCC) adenocarcinoma, and other types account for approximately 10% of cases.[1,7,8] Long-term use of a urinary catheter increases the risk of malignancy from the urethra to the bladder.[9,10] The risk of bladder

cancer was 86.8 per 100,000 person-years in the 10 to 19-year long-term catheter group and increased to 398.1 per 100,000 person-years in the 20-year long-term catheter group. or more (RR 4.6; 95% CI, 1.5-14.0).[1] The duration of catheterization in the patient population ranged from 10 to 26 years, with an average of 17.6 years.[11] Chronic catheterization (adjusted subdistribution HR (sdHR)=4.80, 95% CI: 4.26 to 5.42, p=0.001) was an independent predictor of bladder cancer.[12] Bladder cancer in spinal cord injury (SCI) patients is a widely recognized phenomenon.[13,14] Bladder cancer specifically is the third leading cause of cancer death in the spinal cord injury (SCI) population.[15]

The SCI population has a 25.4 times higher risk of developing bladder cancer compared to the normal population matched for age and sex. For patients with SCI, 1.0% (CI, 0.0% to 5.0%) developed bladder cancer. The inflammatory microenvironment is known to be an important cause of tumor formation. Apart from microinflammation due to the long-term use of a urinary catheter, another cause of bladder cancer is related to the microinflammatory process, namely urinary tract stones. Bladder carcinogenesis is associated with chronic inflammation caused by lipopolysaccharide. However, there have been no systematic review studies that report the incidence of bladder cancer due to the long-term use of urinary catheters. In this study, we wanted to evaluate whether long-term urinary catheter use is an independent risk factor for bladder cancer.[7,16]

Therefore, we aimed to conduct a systematic review of long-term indwelling catheter effects on bladder cancer.

METHODS

Search strategy

We performed a comprehensive search on a topic that assesses long-term indwelling urinary catheterization and bladder cancer with the keywords "long-term indwelling catheter" and "bladder cancer" and its synonyms from electronic databases including Pubmed, Cochrane Central Database, and Scopus (Table 1). The records were then systematically evaluated using inclusion and exclusion criteria. Three researchers (A.P.T., D.D., and A.H.S.) independently performed the initial search, and discrepancies found were resolved by discussion. A preferred reporting item for Systematic Reviews flowchart of the literature search strategy of studies was presented in Figure 1.

Selection criteria

The inclusion criteria for this study are all studies that assess long-term indwelling catheter and bladder cancer in non-SCI patients.

We include all related clinical research/original articles and exclude case reports, review articles, non-English language articles, manuscripts, abstracts only, and studies unrelated to long-term indwelling catheter and bladder cancer.

Data extraction

Data extraction and quality assessment were done by 3 independent authors (A.P.T., D.D., and A.H.S.) using standardized extraction, which includes authors, year of publication, population country, study design, sample size, and follow-up period.

Statistical analysis

We used RevMan version 5.4 software (Cochrane Collaboration). We used the hazard ratio (HR) and a 95% CI as a pooled measure for dichotomous data. The inconsistency index (I2) test, which ranges from 0% to 100%, was used to assess heterogeneity across studies.

A value above 50% or $p<0.05$ indicates statistically significant heterogeneity. We used the inverse variance method with a random effect model. All p values with a statistical significance set at 0.05 or below.

Table 1: Search strategy criteria.

Database searched	Search terms	Limits	Initial search results	Included review
PubMed, Cochrane, and SCOPUS	Indwelling/ long/ continuous/persistent urinary catheterization PLUS bladder/ vesica urinary/ cancer/ tumor	English only	411 (PubMed)+49 (Cochrane)+180 (SCOPUS)=624 duplicated results	6[6-9,12,13]

RESULTS

Study selection

A PRISMA flowchart of the selection of eligible studies is given in Figure 1. A total of 640 studies were retrieved from the initial search, of which 624 were retrieved (after excluding sixteen (16 duplicated studies). After doing abstract screening, six hundred and three (603) studies were excluded due to several reasons (study design not observational studies, and not relevant to the research and outcomes). Finally, twenty one (21) studies were included

in the full-text screening and fifteen (15) were excluded due to not being available as full-text articles, not complete data, and not available in English. Out of the six (6) final studies that were qualified for the systematic reviews analysis.

Study characteristics

A total of 38.719 patients from 2 cohort studies were included. Patients enrolled in this study have different gender characteristics (male 70.04%, female 29.96%) in the Chung Han's study, whereas female 52.3% and male 47.7% in the Amanda's study.

Age ranging from 32 years to 71 years old, as seen in the Table 2.

The control groups from all studies were general populations, age-matched without a history of chronic urinary catheterization.

Analysis showed that chronic indwelling catheterization was significantly increasing the risk of bladder cancer [95% CI, 1.7-13.96%], $p<0.05$, $I2=84\%$ (Figure 1).

It was found that the risk of bias, evaluated through the NOS, resulted in a final score of 4.83, indicating poor quality (Table 4).

This low score could be attributed to the fact that the development of bladder cancer is a complex process that involves various factors and is not well-defined in studies that involve large populations.

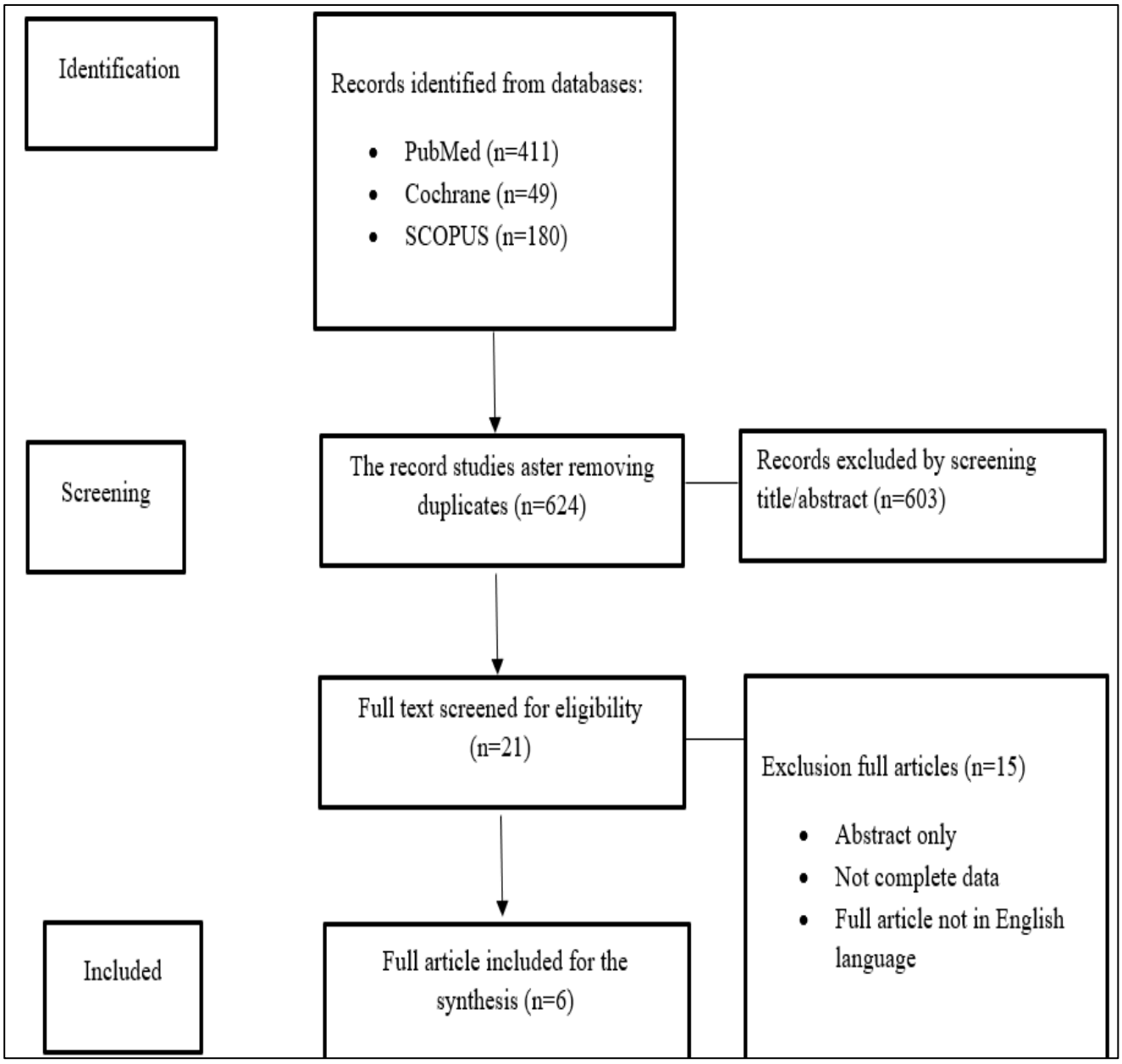


Figure 1: Study flow diagram.

Table 2: Characteristics of the included studies.

Author	Study design	Country	Sample (n)	Age (in years)	Race (Black/ white)	Gender (Male/ female)	Catheterization	Tumor histologic findings	Duration (in years)	Follow up (in years)
Ho et al[8]	Cohort	Taiwan	9.080 (1.816 vs 7.264)	47.42±15.84	N/A	1.272/544 vs 5.088/2176	Chronic indwelling	N/A	N/A	11
Hird et al[12]	Cohort	Canada	147.612 (36.903 vs 110.709)	62 (50-71)	N/A	19.290/17.613 vs 57.870/52.839	Chronic indwelling or chronic intermittent	N/A	2	8.5 (IQR: 4.9-11.7)
West, et al[9]	Retrospective review	Texas	130	57.3±11.5	4/38 vs 8/80	129/1	Chronic indwelling, suprapubic, clean intermittent or condom	TCC, SCC, AC	N/A	N/A
Kalisvaart et al[13]	Retrospective review	California	32	N/A	N/A	N/A	Urethral, external, or intermittent catheter	TCC, SCC, AC, mixed TCC and SCC	N/A	N/A
Pannek[7]	N/A	Germany, Switzerland, Austria	48/ 43.561	53.3±14.7	N/A	29/8	Reflex voiding, intermittent, or indwelling	Superficial, Ca *in situ*, urothelial, SCC	8.5±11.2	N/A
Groah et al[6]	Historical cohort	Denver	3670	48	N/A	2936/734	Spontaneous voiding, intermittent, indwelling, or condom	N/A	N/A	2

Table 3: Chronic indwelling catheterization significantly increasing the risk of bladder cancer.

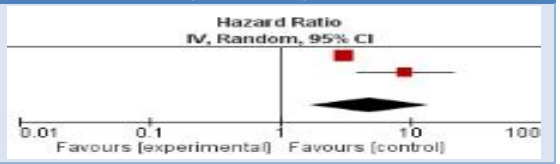
Study or subgroup	Log (Hazard ratio)	SE	Weight	Hazard ratio IV, random, 95% CI	Hazard ratio IV, Random, 95% CI
Hird et al[12]	1.1217	0.0828	57.6%	3.07 [2.61, 3.61]	
Ho et al[8]	2.2094	0.4329	42.4%	9.11 [3.90, 21.28]	
Total (95% CI)			100%		
Heterogeneity: Tau=0.49; Chi 2=6.09, df=1 (p=0.01); I2=84%					
Test for overall effect: Z=2.94 (p=0.003)					

Table 4: Bias assessment using NOS cohort..

Study	Number of stars			
	Selection*	**Comparability****	**Exposure*****	**Overall**
Han et al[8]	4	2	2	8/9
Hird et al[12]	3	2	3	8/9
West et al[9]	2	1	1	4/9
Kalisvaart et al[13]	1	0	0	1/9
Pannek[7]	1	1	0	2/9
Groah et al[6]	4	2	0	6/9

*Maximum 4 stars, **Maximum 2 stars and ***Maximum 3 stars

DISCUSSION

One of the causes of mortality in men throughout the world is bladder cancer. Chronic indwelling urinary catheter (CIDC) is a risk factor for bladder cancer, especially in patients with spinal cord injury (SCI). Several risk factors for bladder cancer are men, old age, smoking, exposure to toxic chemicals, medications (long-term cyclophosphamide), and spinal cord injury (SCI).[7,12,17,18] Exposure to tobacco smoke increases rates of epigenetic methylation of promoter genes and inactivation of tumour suppressor genes, resulting in poorer outcomes.[19] Other risk factors according to research by Jurgen et al, are genetic factors, long-term use of catheters, bladder stones, and male gender.[6]

Most previous studies have shown that the relative risk of bladder malignancy in the spinal cord injury population is 16-28 times higher than in the general population.[13] Chronic catheterization (sdHR 4.80; 95% CI; 4.26 to 5.42; p<0.001) and number of UTIs (sdHR 1.04; 95% CI; 1.04 to 5.41; p<0.001) are an independent factor of bladder cancer.[12] Indwelling catheter users had a significantly greater risk of bladder cancer (relative risk [RR] 4.9; 95% CI, 1.3-13.8) than those using non-indwelling methods.[1] This is similar to our findings, where an indwelling catheter increases the probability of bladder cancer by 4.87% (95% confidence interval (CI), 1,7-13,96%, I2=84% (Table 3). Insertion of an indwelling catheter has a significant effect on the incidence of bladder cancer (p=0.003)

Spinal cord injury is reported to be a risk factor for bladder cancer, especially the squamous cell type. Several reports are saying that the incidence of bladder cancer is higher in the SCI group than in the general group, but only limited to descriptive or cross-sectional studies. Groah et al's research stated that the SCI population group had a 2.54 higher risk of suffering from bladder cancer according to age and sex compared to the general group.[1] Similar to the Groah study, the SCI group had an incidence of bladder cancer that was 5.74 and 8.55 times greater than the control group.[7]

Age

The mean age of the study population was 47.42±15.84. Although extremely rare, bladder cancer can be seen in children and young adults and usually presents with a low-grade and noninvasive disease.[20] The average age of onset of bladder cancer is 51 years, and the earliest bladder cancer occurs 13 years post-SCI. Similarly, we noted that the median age at diagnosis of bladder cancer was 48 years.[1] Patients in the 45 and 60 year age categories in the CIDC-non-SCI group had a 21.37 higher risk of bladder cancer compared to the control group, while the 60 year age group had a significantly higher risk of bladder cancer in the CIDC-non-SCI group 3.8%.[7] The mean age at diagnosis was 57.3 years (range 36 to 84 years), which is about 10 years earlier than expected in the general population. This is similar to our findings, where the average age is in the fifth to sixth decades. This suggests a disease progression that takes decades after exposure to extrinsic factor.[8]

Gender

Gender is a well-documented risk factor for bladder cancer in the general population, with men having almost 4 times the risk than women.[1] Bladder cancer is around four times more likely to be diagnosed in men than women. Mortality is likewise around four times greater in men.[20] Most SCI and CIDC-non-SCI patients are men (70%). The risk of bladder cancer was 5.84 and 7.57-fold higher in the SCI and CIDC-non-SCI groups compared to the control group, respectively.[7] Reasons for the disparity in gender incidence and mortality include differences in hormonal profiles (activity of the sex steroid hormone pathway). Bladder cancer risk has been observed to be lower in women with older age at menarche, parity compared to nulliparous women. Enzymes involved in the degradation of aromatic amines and the detoxification of foreign materials are associated with the metabolism of bladder carcinogens. The expression of this enzyme is expressed differently in men and women. AR expression appears to be downregulated in immunohistochemical investigations of bladder cancer, and this downregulation tends to increase with increasing tumor stage and grade.[8]

Histologic findings

Based on Jugen et al research, squamous cell cancer is the second most diagnosed cancer. In patients with chronic catheterization, SCC is the dominant malignant bladder tumor.[6] The general population has a much higher proportion of SCC compared to transitional cell carcinoma (TCC).[13] In contrast to the study of Kalisvaart et al the histological type of TCC was the predominant histological finding (55%) identified in this study. It has been reported that SCC is the most common tumor type. Smoking is reported to increase the risk of bladder cancer up to 4 times, especially the TCC type. SCC occurs more frequently in patients using urethral catheters than in patients using clean intermittent catheterization, condom catheterization, or spontaneous voiding.[9]

Follow-up period

Patients with chronic urinary catheterization for more than 2.9 years have the highest risk of bladder cancer.[12] During the follow-up period, bladder cancer cases were higher in the CIDC-non-SCI group 0.88% (16/1816) compared to the SCI group 0.55% (10/1816) and significantly different from the control group 0.11% (8/7264). The incidence rate of bladder cancer was 68.90 and 102.53 per 100,000 people per year in the SCI and CIDC-non-SCI groups, respectively, so the incidence rate of bladder cancer was higher in the CIDC-non-SCI group. Patients with a history of SCI (HR 6.51; 95% CI, 2.56-15.62) or CIDC without SCI (HR 9.11; 95% CI 3.9-21.29) had a higher rate of

bladder cancer compared with the reference cohort. The risk of bladder cancer is higher, especially in men and the elderly.[7] The group with the use of IDC has a 25-fold greater risk of bladder cancer compared to the general population with use for 12 years or more.[1] Bladder cancer is more prevalent among people under the age of 60. The root cause of tumor formation is a microinflammatory environment, where infections and inflammation are commonly found in both symptomatic and non-symptomatic CIDC patients. Conditions such as urinary tract stones and long-term catheters are often the main reasons related to the inflammation.[7] Insertion of a catheter causes mechanical changes to the bladder. Dysplasia and metaplasia are considered precursors of bladder cancer.[6]

Outcomes

More severe bladder cancer complications have been associated with chronic use of indwelling catheters. The rate of development of SCC in patients with chronic catheters is estimated to be 12-14%, with the rate of squamous changes in the bladder mucosa reaching 80%.[21] One theory suggests that chronic irritation and infection associated with the indwelling catheter in the bladder lead to the development of bladder malignancy, where an eosinophilic inflammatory response with urothelial dysplasia and squamous metaplasia occurs at the catheter insertion site. According to a large population-based cohort study of 147,612 patients, 1.1% of patients with chronic or intermittent bladder catheterization were at risk of developing bladder cancer. Histopathological changes include keratinizing squamous metaplasia in a quarter of patients with chronic bladder catheters. Chronic inflammatory processes lead to the development of histologically more aggressive subtypes of bladder cancer, particularly SCC. Bladder carcinogenesis can also result from the influence of heat-killed Escherichia coli or chronic inflammation due to lipopolysaccharide. Animal models have demonstrated that there is an increased production of nitrosamine during infection of Escherichia coli and causes urothelial hyperplasia and neoplasia.[18] Lack of physical activity has been reported to be associated with bladder cancer. In post-SCI (spinal cord injury) conditions, patients are more susceptible to chronic bladder infections and inflammation.[7]

Limitation

The studies collected are limited, but the sample size is quite large. In addition, the risk factors for bladder cancer are relatively different in each journal. This causes the data to tend to be biased. There is also a lack of information such as the hazard ratio and control variable used, so we could not include calculating the hazard ratio. There were several studies with relevant titles, but we did not have further access to know the content of those studies, so we could not include those for our report. More research, especially RCTs, should be pursued to clarify this issue and achieve a better result.

CONCLUSION

A long-term indwelling catheter significantly increases the risk of bladder cancer in non-SCI patients due to chronic inflammation.

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